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Angiotensin II receptor blockade prevents acute renal sodium retention induced by low levels of orthostatic stress

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Angiotensin II receptor blockade prevents acute renal sodium retention induced by low levels of orthostatic stress.

Background. Depending on its magnitude, lower body negative pressure (LBNP) has been shown to induce a progressive activation of neurohormonal, renal tubular, and renal hemodynamic responses, thereby mimicking the renal responses observed in clinical conditions characterized by a low effective arterial volume such as congestive heart failure. Our objective was to evaluate the impact of angiotensin II receptor blockade with candesartan on the renal hemodynamic and urinary excretory responses to a progressive orthostatic stress in normal subjects.

Methods. Twenty healthy men were submitted to three levels of LBNP (0, −10, and −20 mbar or 0, −7.5, and −15 mm Hg) for 1 hour according to a crossover design with a minimum of 2 days between each level of LBNP. Ten subjects were randomly allocated to receive a placebo and ten others were treated with candesartan 16 mg orally for 10 days before and during the three levels of LBNP. Systemic and renal hemodynamics, renal sodium excretions, and the hormonal response were measured hourly before, during, and for 2 hours after LBNP.

Results. During placebo, LBNP induced no change in systemic and renal hemodynamics, but sodium excretion decreased dose dependently with higher levels of LBNP. At −20 mbar, cumulative 3-hour sodium balance was negative at –2.3 ± 2.3 mmol (mean ± SEM). With candesartan, mean blood pressure decreased (76 ± 1 mm Hg vs. 83 ± 3 mm Hg, candesartan vs. placebo, $P < 0.05$) and renal plasma flow increased (858 ± 52 mL/min vs. 639 ± 36 mL/min, candesartan vs. placebo, $P < 0.05$). Glomerular filtration rate (GFR) was not significantly higher with candesartan (127 ± 7 mL/min in placebo vs. 144 ± 12 mL/min in candesartan). No significant decrease in sodium and water excretion was found during LBNP in candesartan-treated subjects. At –20 mbar, the 3-hour cumulative sodium excretion was + 4.6 ± 1.4 mmol in the candesartan group ($P = 0.02$ vs. placebo).

Conclusion. Selective blockade of angiotensin II type 1 (AT_1) receptors with candesartan increases renal blood flow and prevents the antinatriuresis during sustained lower body negative pressure despite a modest decrease in blood pressure. These results thus provide interesting insights into potential benefits of AT_1 receptor blockade in sodium-retaining states such as congestive heart failure.

Key words: lower body negative pressure, sodium, sympathetic nervous system, renin-angiotensin-aldosterone system, candesartan, AT_1 receptor blocker.

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Chronic sodium-retaining edema-forming states such as heart failure, the nephrotic syndrome, and hepatic cirrhosis are characterized by avid renal sodium and water retention, which have been attributed to a low effective arterial volume [1]. These disease states feature circulatory and volume control abnormalities characterized by an activation of several neurohormonal systems, including sympathetic nerve activity and the renin-angiotensin-aldosterone and the vasopressin systems. These hormonal systems influence renal function through their actions on renal hemodynamics and water and electrolytes transport across tubular cells [2].

In patients with heart failure, the renal response to the low effective arterial volume is characterized by a marked sodium retention, which leads to an undesirable vicious circle contributing to a further deterioration of the disease [3]. Blockade of the renin-angiotensin system with angiotensin-converting enzyme (ACE) inhibitors or selective angiotensin II receptor antagonists has been shown to reduce the morbidity and mortality in patients with congestive heart failure [4–7]. The beneficial effects of these agents in heart failure have been attributed to the reductions in preload and afterload as well as to the amelioration of the hormonal profile both factors improving cardiac output.

In heart failure, blockers of the renin-angiotensin system could also lead to a clinical improvement through a direct effect on renal function, independently of their ability to modulate cardiac function. Indeed, ACE inhibitors as well as angiotensin II antagonists have been shown to increase urinary sodium excretion in normotensive and hypertensive subjects [8]. Blockers of the renin-angiotensin system have also been found to improve the ability to excrete acute and chronic sodium loads in

animal models of congestive heart failure [9, 10]. The purpose of the present study was to evaluate the clinical impact of angiotensin II receptor blockade on the renal hemodynamic and excretory responses to a progressive orthostatic stress in normotensive subjects. To test this hypothesis, we have used the model of sustained lower body negative pressure in normotensive subjects pretreated randomly either with a placebo or with the angiotensin II receptor antagonist candesartan. We have shown previously that the application of a 1-hour lower body negative pressure (LBNP) step-wise stimulates the sympathetic nervous system and the renin-angiotensin system leading to a decrease in urinary sodium and water excretion before any changes in renal blood flow and glomerular filtration rate (GFR) are observed [11]. Thus, this model enables to mimic in normal subjects the hemodynamic conditions to which the kidneys are exposed during a progressive reduction of cardiac preload leading to an activation of both the sympathetic nervous system and the renin-angiotensin system.

METHODS

Twenty healthy normotensive subjects without any clinical history of vasovagal syncope, orthostatic hypotension, clinical or laboratory evidence of heart, liver, kidney, and endocrine diseases were included in this study. Their mean age was 24.2 years (range 20 to 31 years). Their mean height was 176 cm (range 166 to 189 cm) and mean weight 73.3 kg (range 55 to 88 kg). A full medical history and a complete physical examination, including an orthostatic test, were performed before inclusion. The protocol was approved by the local hospital ethical committee, and written informed consent was obtained from each subject.

Study design

This was a randomized double-blind parallel group (placebo vs. candesartan) study. Each subject was initially randomized to receive either 16 mg of candesartan once a day or a placebo for 14 days (from day 1 to day 14). On days 10, 12, and 14 of the treatment, each volunteer was investigated before, during, and after stimulation with one of three levels of LBNP (0, −10, and −20 mbar) for 1 hour according to a triple crossover design. The –10 and 20 mbar values correspond to −7.5 and −15 mm Hg. Each LBNP study day was separated by 48 hours and subjects remained on treatment. The dose of candesartan 16 mg or placebo was given orally every morning at 8:00 a.m. The control phase (0 mbar) was randomized within each sequence and the lower level of LBNP was always tested before the higher level. All subjects received a fixed sodium diet (130 mmol sodium/day) provided by the hospital from day 6 to day 14. Water intake was allowed ad libitum. A series of 24-hour urine collections were performed on days 8, 9, 11, and 13 to monitor the compliance to the diet and to evaluate the baseline sodium, potassium, and creatinine excretions. Subjects were asked to refrain from smoking and drinking caffeine-containing and alcoholic beverages from day 8 to day 14.

After an overnight fast, the volunteers were installed in supine position during each whole study day, except for voiding. An infusion of inulin and para-aminohippurate (PAH) was started to measure GFR and renal plasma flow (RPF). A light breakfast and an oral water load of 5 mL/kg were ingested before 8.00 a.m. Subsequently, subjects received a fixed amount of water (150 mL/hour) to maintain a stable urine output. After 3 hours of equilibration (T-240 to T-60), the study days were divided into 1 hour of baseline (T-60 to T0), 1 hour of LBNP (T0 to T60) and 2 hours of recovery (R1 and R2) (T60 to T120 and T120 to T180). LBNP was applied with subjects in the supine position in a solid plexiglas box sealed tightly around the iliac crests, below the level of the kidneys. A footplate was inserted in the box to prevent inward movement of the volunteers. The 1-hour LBNP was not interrupted to allow subjects to void.

Vital signs (blood pressure, heart rate) were recorded using an automated monitor placed on the left arm (Lifesign Monitor; WelchAllyn, Skaneateles Falls, NY, USA). Measurements were done every 5 minutes from time T-30 to T120 and every 15 minutes from T-120 to T-30 and T120 to T180. Urine was collected hourly throughout the study to measure urine output, urinary electrolyte excretion (sodium, potassium, endogenous trace lithium, and uric acid) and to evaluate the changes in GFR and RPF. The same parameters were measured hourly in the plasma. Blood was collected on times T0, T60, and T120 for the measurements of plasma norepinephrine, aldosterone, and plasma renin activity (PRA).

Analytic methods

Urinary and plasma sodium and potassium were measured by flame photometry (IL-943) (Instrumentation Laboratory, Milan, Italy) and creatinine by the picric acid method (Cobas-Mira; Roche AG, Basel, Switzerland). Plasma and urinary inulin and PAH were determined by photometry (Autoanalyzer II-Technicon; Bran & Luebbe, Norderstedt, Germany). Endogenous trace lithium was measured by atomic absorption spectrophotometry. This method, which does not necessitate the administration of lithium, has been validated in several previous clinical studies [12–15]. PRA [16], plasma aldosterone [17], and plasma catecholamines [18] were determined as described previously.

Urinary electrolytes excretion rate was calculated as $U_x \cdot V$ (μmol/min) and clearances (mL/min) using the standard formula $C_x = U_x \cdot V/P_x$ where U_x and P_x are the

Table 1. Blood pressure and heart rate responses to lower body negative pressure (LBNP) during candesartan and placebo

	LBNP 0			LBNP-10			LBNP-20		
	Baseline	LBNP	Recovery	Baseline	LBNP	Recovery	Baseline	LBNP	Recovery
Systolic blood pressure *mm Hg*									
Placebo ($N = 10$)	114 ± 3	114 ± 3	117 ± 2	117 ± 4	121 ± 2	120 ± 3	113 ± 4	114 ± 2	116 ± 3
Candesartan ($N = 10$)	111 ± 2	115 ± 3	112 ± 2	109 ± 2^{a}	111 ± 1^{b}	111 ± 1^{a}	107 ± 1	109 ± 2	110 ± 2
Diastolic blood pressure *mm Hg*									
Placebo ($N = 10$)	65 ± 2	67 ± 3	69 ± 20	66 ± 3	71 ± 2^{c}	70 ± 2	64 ± 2	68 ± 3^{d}	69 ± 2
Candesartan ($N = 10$)	61 ± 2	63 ± 2	62 ± 2^{a}	60 ± 10^{a}	$63 \pm 2^{b,c}$	63 ± 1^{a}	59 ± 1	62 ± 2^{d}	61 ± 2^{a}
Mean blood pressure *mm Hg*									
Placebo ($N = 10$)	82 ± 2	82 ± 3	85 ± 2	83 ± 3	87 ± 2	86 ± 2	80 ± 3	83 ± 2	85 ± 2
Candesartan ($N = 10$)	78 ± 2	81 ± 2	78 ± 1^{a}	76 ± 1^{b}	79 ± 1^{b}	79 ± 1^{b}	75 ± 1	78 ± 2	77 ± 2^{a}
Heat rate *beats/min*									
Placebo ($N = 10$)	61 ± 3	56 ± 3^{d}	57 ± 3	64 ± 4	60 ± 3^{d}	59 ± 4	64 ± 3	60 ± 3^{d}	57 ± 3
Candesartan ($N = 10$)	60 ± 2	59 ± 3	57 ± 3	61 ± 3	59 ± 3	56 ± 2	60 ± 3	59 ± 3	56 ± 3

Values are mean ± SEM.
[a] $P < 0.05$; [b] $P < 0.01$ candesartan vs. placebo during same period; [c] $P < 0.05$; [d] $P < 0.01$ LBNP vs. baseline.

urine and plasma concentrations of x and V is the urine flow rate in mL/min. Filtration fraction was calculated by dividing the GFR by the RPF. Renal vascular resistances were calculated as mean blood pressure divided by the renal blood flow, this latter being calculated from renal plasma flow and hematocrit.

Statistics

All results are expressed as means ± SEM. Within group analysis were performed using a one-way analysis of variance (ANOVA) analysis followed by a Dunnett test comparing the LBNP period to the baseline period and the two recovery periods (R1 and R2). Intergroup comparisons were analyzed using a Student *t* test except for the analysis of cumulated sodium excretion were the two groups were compared using the Mann-Whitney test. Values with a $P < 0.05$ were considered as statistically significant.

RESULTS

All volunteers completed the study (ten in each group). The two levels of LBNP were well tolerated with no syncope nor presyncopal signs and symptoms observed throughout the study. Screening characteristics (age, height, weight, systolic blood pressure, diastolic blood pressure, and pulse) were similar for the two groups. Twenty-four–hour urinary sodium excretion before and between study days was similar in the placebo group (112 ± 6 mmol/day) and in the candesartan (110 ± 7 mmol/day).

Systemic and renal hemodynamic responses to LBNP

At baseline, the heart rate was similar in both groups whereas systolic and diastolic blood pressures were generally lower in the candesartan group (Table 1). During LBNP and the recovery periods, no significant change in systolic blood pressure was observed. In contrast, diastolic blood pressure increased significantly during LBNP at –10 and –20 mbar. Heart rate decreased during LBNP but the changes were similar in the three levels of LBNP.

As shown in Figure 1, the RPF was significantly higher in the candesartan group than in the placebo group and the GFR was slightly but not significantly higher in the candesartan group. The GFR, the RPF and the renal vascular resistance did not change throughout the study in the placebo group. In contrast, the renal vascular resistance increased (from 0.047 ± 0.003 mm Hg/mL/min to 0.057 ± 0.004 mm Hg/mL/min, $P < 0.05$) and the RPF decreased (from 909 ± 61 mL/min to 746 ± 46 mL/min, $P < 0.05$) during the LBNP period at –20 mbar in the candesartan group. The fall in RPF at –20 mbar averaged $-17 \pm 3\%$ in the candesartan and $-9 \pm 5\%$ in the placebo group ($P =$ NS). Consequently the filtration fraction rose significantly during this period (from $16.2\% \pm 0.8\%$ to $19.0\% \pm 1.1\%$). Yet, at the end of the −20 mbar LBNP period, RPF was still higher in the candesartan group than in the control group.

Neurohormonal responses during the LBNP and recovery periods

The hormonal response to LBNP is presented in Figure 2. At baseline, the hormone profile was similar in the two groups except for PRA, which, as expected, was higher in the candesartan group. Aldosterone was slightly but not significantly lower in the candesartan group. During LBNP, no change in plasma norepinephrine levels was found in either groups at 0 and –10 mbar. At –20 mbar an increase in norepinephrine was found in both groups but the change did not reach the statistical significance. PRA and aldosterone levels increased as the negative pressures became stronger only in the placebo group.

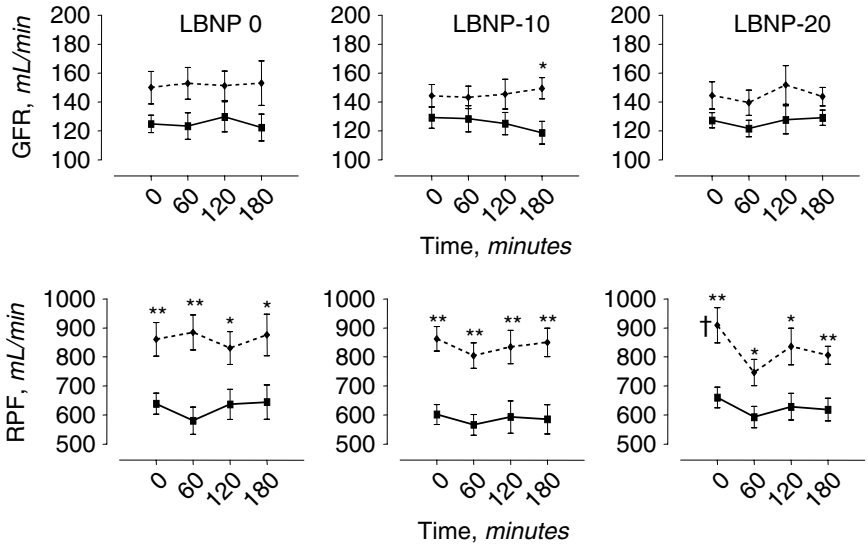

Fig. 1. Effects of three levels of lower body negative pressure (LBNP) on glomerular filtration rate (GFR) and renal plasma flow (RPF) in normotensive subjects who received either candesartan 16 mg/day (dash lines) or a placebo (solid lines) for 10 days. LBNP-10 and LBNP-20 indicate, respectively, –10 mbar (−7.5 mmHg) and −20 mbar (−15 mm Hg) of LBNP. LBNP was applied from 0 to 60 minutes. $^{*}P < 0.05$; $^{**}P < 0.01$ candesartan vs. placebo at the same time; †$P < 0.05$ time 0 vs. time 60 minutes. Values are means ± SEM.

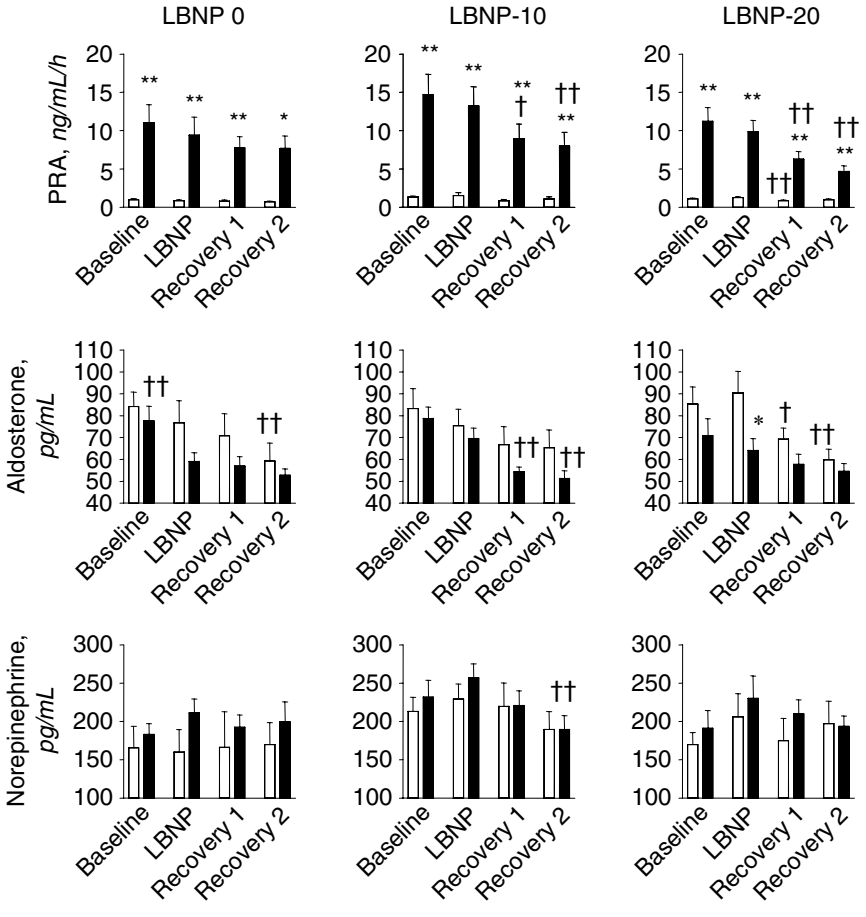

Fig. 2. Effects of three levels of lower body negative pressure (LBNP) on plasma renin activity (PRA) and plasma aldosterone and plasma norepinephrine levels in normotensive subjects who received either candesartan 16 mg/day (■) or a placebo (□) for 10 days. LBNP-10 and LBNP-20 indicate, respectively, −10 mbar (−7.5 mm Hg) and −20 mbar (−15 mm Hg) of LBNP. $^{*}P < 0.05$; $^{**}P < 0.01$ candesartan vs. placebo at the same time; †$P < 0.05$; ††$P < 0.01$ vs. LBNP period.

Renal tubular response to LBNP

The changes in urinary water and electrolytes excretion are presented in Table 2. In the placebo group, the changes in urine output and electrolyte excretion were the most pronounced during the –20 mbar LBNP period when the suction on the limbs was stronger. The LBNP-induced changes were characterized by a decrease in urine output and sodium excretion and a fall in lithium clearance suggesting a decrease in the proximal reabsorption of sodium. The decrease in potassium was also slightly more pronounced at –20 mbar than at the two other levels of LBNP. In the placebo group, sodium

Table 2. Renal tubular response to lower body negative pressure (LBNP) in subjects receiving either a placebo or candesartan

	LBNP T0			LBNP T10			LBNP T20		
	Baseline	LBNP	Recovery	Baseline	LBNP	Recovery	Baseline	LBNP	Recovery
UV *mL/min*									
Placebo ($N = 10$)	2.90 ± 0.44	2.48 ± 0.32	2.88 ± 0.44	2.70 ± 0.38	2.55 ± 0.33	2.69 ± 0.43	2.91 ± 0.46	2.21 ± 0.33	2.37 ± 0.28
Candesartan ($N = 10$)	3.02 ± 0.41	3.50 ± 0.73	2.91 ± 0.37	2.49 ± 0.46	3.12 ± 0.38	3.36 ± 0.41	2.72 ± 0.45	2.30 ± 0.31	3.6 ± 0.29^{a}
$U_{Na}V$ µ*mol/min*									
Placebo ($N = 10$)	102 ± 12	84 ± 11	95 ± 11	89 ± 15	74 ± 12	93 ± 13	107 ± 20	70 ± 8^{b}	104 ± 14
Candesartan ($N = 10$)	103 ± 23	93 ± 30	95 ± 11	85 ± 12	72 ± 11	113 ± 13^{c}	95 ± 15	93 ± 18	119 ± 16^{d}
FENa %									
Placebo ($N = 10$)	0.59 ± 0.07	0.52 ± 0.09	0.54 ± 0.07	0.53 ± 0.1	0.40 ± 0.07	0.51 ± 0.06	0.58 ± 0.09	0.42 ± 0.05^{b}	0.59 ± 0.19^{c}
Candesartan ($N = 10$)	0.49 ± 0.08	0.42 ± 0.09	0.51 ± 0.09	0.44 ± 0.08	0.35 ± 0.06	0.54 ± 0.07^{c}	0.45 ± 0.05	0.47 ± 0.06	0.56 ± 0.06^{d}
$U_{K}V$ µ*mol/min*									
Placebo ($N = 10$)	96 ± 15	92 ± 11	70 ± 6	99 ± 13	93 ± 13	75 ± 9^{c}	96 ± 9	83 ± 9	74 ± 7
Candesartan ($N = 10$)	96 ± 15	103 ± 15	71 ± 10^{d}	98 ± 9	100 ± 11	71 ± 12^{c}	91 ± 9	96 ± 10	75 ± 9^{d}
Cl_{Li} *mL/min*									
Placebo ($N = 10$)	24.1 ± 2.5	25.2 ± 2.1	23.4 ± 1.5	27.3 ± 2.1	26.8 ± 2.6	25.8 ± 1.8	30.0 ± 2.5	22.3 ± 2.2^{b}	23.6 ± 1.5
Candesartan ($N = 10$)	31.1 ± 2.7	28.0 ± 2.1	26.0 ± 1.8	31.8 ± 2.2	29.7 ± 1.9	30.0 ± 2.6	29.4 ± 1.2	26.1 ± 1.7	27.0 ± 2.2

Values are mean ± SEM. Abbreviations are: UV, urine output; $U_{Na}V$, sodium excretion; FENa, fractional excretion of sodium, $U_{K}V$, potassium excretion; Cl_{Li}, lithium clearance.
[a] $P < 0.01$ candesartan vs. placebo during same period; [b] $P < 0.05$ vs. baseline; [c] $P < 0.01$; [d] $P < 0.05$ LBNP vs. recovery period.

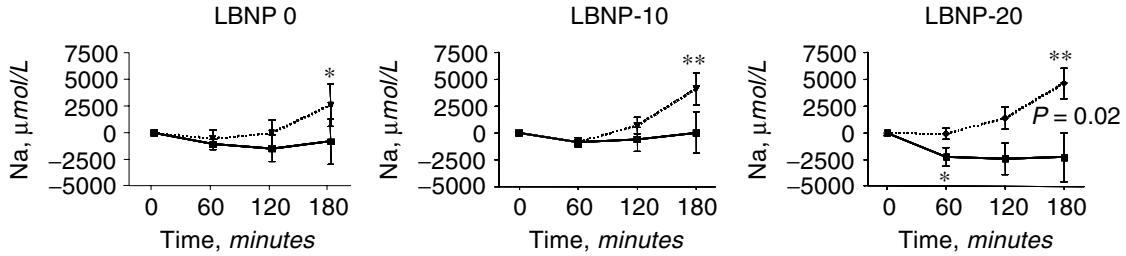

Fig. 3. Effects of three levels of lower body negative pressure (LBNP) on cumulative urinary sodium excretion in normotensive subjects who received either candesartan 16 mg/day (dash lines) or a placebo (solid lines) for 10 days. LBNP-10 and LBNP-20 indicate, respectively, −10 mbar (−7.5 mm Hg) and −20 mbar (−15 mm Hg) of LBNP. $^{*}P \leq 0.05$; $^{**}P \leq 0.01$ vs. time 0.

excretion came back to the baseline during the first recovery period whereas the effect of LBNP on urine flow rate and lithium clearance persisted until the second recovery period.

In the candesartan group, a nonsignificant decrease in urine flow rate was also observed during the –20 mbar LBNP period. However, no significant decrease in urinary sodium and potassium excretions and endogenous lithium clearance were found during LBNP in subjects receiving candesartan. More interestingly, marked increases in urine output and sodium excretion were observed during the first and second recovery periods, suggesting a rebound effect as soon as the LBNP was removed. This rebound effect was strongest at –20 mbar but was also present at –10 mbar. Figure 3 shows the cumulative sodium excretion during the LBNP and the two recovery periods in the two groups. The figure clearly shows that subjects receiving candesartan maintain their ability to excrete sodium at all levels of LBNP, whereas in the control group, LBNP induces a level-dependent decrease in cumulative sodium excretion. At –20 mbar, the cumulative sodium excretion was significantly greater under candesartan than under placebo ($P = 0.02$).

DISCUSSION

The purpose of the present study was to characterize the effects of angiotensin II receptor blockade on the renal response to a sustained orthostatic stress in men. Our results show that candesartan lowers blood pressure and increases RPF in normal subjects. Angiotensin II receptor blockade also induced a greater renal hemodynamic response to orthostatic stress leading to a greater decrease in renal plasma flow at a LBNP of –20 mbar (−15 mm Hg). However, despite the decrease in renal perfusion, subjects receiving the angiotensin II receptor antagonist maintain their capacity to excrete sodium during the orthostatic stress as candesartan reversed the antinatriuretic response of the placebo into a natriuretic response.

Several previous studies have demonstrated in normal subjects that low levels of LBNP (below −20 mm Hg) do not affect renal hemodynamics, whereas the application of a more prolonged and/or more intense LBNP leading to an unloading of both arterial and cardiopulmonary baroreceptors produce a decline in GFR and RPF [19–22]. In accordance with these earlier observations, no significant change in renal hemodynamics was found during LBNP in the placebo group. In contrast, a significant fall in RPF and an increase in renal vascular resistance were observed at –20 mbar (−15 mm Hg) in subjects receiving candesartan. Our experiment suggests that the renal hemodynamic response to LBNP leading to a decrease in renal perfusion is shifted to lower levels of LBNP when the renin-angiotensin system is blocked resulting in an inability to actively compensate for the orthostatic stress. This could be due to an increased sensitivity to the stimulation of efferent renal sympathetic nerve activity or to the activation of other vasoconstrictor systems such as vasopressin or endothelin even though angiotensin II type 1 (AT_1) receptor blockers have been found to decrease sympathetic nerve activity in the kidney [23]. Such an increased sensitivity is in line with earlier findings in animal models in which blockade of the renin-angiotensin cascade resulted in an increased vascular responsiveness to sympathetic and vasopressin stimulation in order to maintain blood pressure and organ perfusion [24]. Our observations are also partially in accordance with the recent report from Frank et al [22] who found a decrease in RPF in a group of subjects treated with eprosartan, with no change in GFR at –15 mm Hg. However, they did find a decrease in RPF in the control group, which we did not observe in the present as well as in previous studies at similar levels of LBNP. The difference between the two studies was the duration of the stimulation (30 minutes in the study by Frank et al vs. 60 minutes in our study) and a possible difference in the kinetics of the two drugs, eprosartan being an AT_1 antagonist with a shorter duration of action than candesartan. It has also been suggested that eprosartan has a more pronounced effect on sympathetic nerve activity than other angiotensin II receptor antagonists [25]. This could also contribute to explain the difference between the two studies.

Although RPF decreased during LBNP at –20 mbar, renal perfusion remained adequate during angiotensin II receptor blockade because candesartan increased RPF at baseline. Thus, even at the end of the –20 mbar period RPF was higher in the candesartan than in the placebo group. This favorable hemodynamic effect of candesartan is in accordance with previous studies, which have demonstrated that angiotensin II receptor blockade leads to a renal vasodilatation in humans [22] or restoration of normal RPF in asymptomatic heart failure patients [8].The candesartan-induced slight but nonsignificant increase in GFR in normotensive subjects is more of a surprise but candesartan has been found to increase GFR in animal models [26–28] as well as in hypertensive patients at the dose of 16 mg [29–31]. In other studies, however, no change in GFR was found after administration of candesartan [32, 33].

The major observation of this study is that sodium excretion is maintained during LBNP despite the transient decrease in RPF and is even increased during the recovery period in the candesartan group. Thus, during the 3 hours of investigations, the cumulative sodium excretion was significantly enhanced with the administration of candesartan. In the control group, the decrease in sodium and water excretion observed at –20 mbar (−15 mm Hg) was comparable to that obtained previously in the same experimental conditions. Interestingly, the sodium retention was due mainly to an increased reabsorption of sodium in the proximal tubule as indicated by the significant fall in lithium clearance during LBNP confirming thereby our initial finding [11]. During angiotensin II receptor blockade, neither the sodium excretion nor the lithium clearance was affected by the orthostatic stress. Initially, we had postulated that both the renin-angiotensin and the sympathetic nervous systems contribute to the proximal sodium retention since both systems have been reported to modulate sodium transport in the proximal nephron [2]. The present findings tend to confirm our hypothesis. To our knowledge, only experiments in animal models have examined the mechanism or the relative contribution of each system to this favorable antinatriuretic effect and have found that angiotensin II receptor blockade improves cardiac baroreflex regulation of renal sympathetic nerve activity leading to an improved ability to excrete sodium [10, 34].

In our experimental conditions, the natriuretic response to angiotensin II receptor blockade was particularly pronounced during the two recovery periods. The natriuresis was observed at –10 mbar as well as at –20 mbar and was associated in both cases with a significant decrease in plasma aldosterone levels. Hence, a decreased reabsorption of sodium and water beyond the proximal tubule may also contribute to the natriuresis at least during the recovery phase. The early recovery period is characterized by the shift of the volume pooled in the extremities to the central circulation. Our data suggest that blockade of the renin-angiotensin system improves the ability of the kidneys to enhance water and sodium excretion during this acute redistribution of volume. This observation may be of clinical relevance as the recovery period in a certain way mimics the redistribution of volume occurring in heart failure when patients go from the standing to the supine position, during nighttime, for example. Our observation would indicate that blockade of the renin-angiotensin system also contributes to improve patients suffering from heart failure by enhancing their

ability to excrete water and sodium in supine position, which has been shown in animal models of heart failure [9].

Taken together, the results of the present study provide new insights into the role of the renin-angiotensin system in regulating renal hemodynamics and sodium excretion during a mild orthostatic stress. More important, they show that angiotensin II receptor blockade enables to maintain renal sodium excretion when the orthostatic stress is applied but also soon after its relieve. This finding may contribute to explain the favorable impact of interrupting the activity of the renin-angiotensin cascade in patients with congestive heart failure in whom large shifts of effective arterial volume occur depending on the position.

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